Journal of Surgical Oncology 2000;73:109–114

Transarterial Chemoembolization for Inoperable Hepatocellular Carcinoma and Postresection Intrahepatic Recurrence

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Background and Objectives: The role of transarterial chemoembolization (TACE) for inoperable hepatocellular carcinoma (HCC) has remained controversial, and its efficacy for postresection intrahepatic recurrence has not been fully assessed. A study was performed to evaluate the treatment results and prognostic factors of TACE treatment in these patients.
Methods: Clinicopathologic data and treatment results of 384 patients with inoperable HCC and 100 patients with postresection recurrent HCC treated with TACE were collected prospectively and analyzed.
Results: TACE was associated with an overall treatment morbidity rate of 23% (112/484) and mortality rate of 4.3% (21/484). A particularly high mortality rate of 20% (9/45) was observed among patients with tumors > 10 cm and pretreatment serum albumin level ≤ 35 g/L. The overall 1-year, 3-year, and 5-year survival rates from the time of first TACE treatment were 49%, 23%, and 17% respectively. Tumor size ≤ 10 cm and serum albumin level > 35 g/L were independent favorable prognostic factors. TACE in patients with postresection recurrent HCC was associated with less morbidity, mortality, and a better survival outcome compared with patients with primary inoperable HCC, but this was largely related to smaller tumor size and better liver function in the former group at the time of TACE treatment.
Conclusions: TACE in patients with inoperable HCC was associated with significant morbidity and mortality, and the survival benefit was limited. Better patient selection in terms of tumor size and liver function may improve treatment results. Patients who have a tumor > 10 cm and poor liver function (serum albumin ≤ 35 g/L) may not be suitable candidates for TACE treatment.
J. Surg. Oncol. 2000;73:109–114.

KEY WORDS: **hepatocellular carcinoma; inoperable; recurrence; transarterial chemoembolization**

INTRODUCTION

Transarterial oily chemoembolization (TACE) is a widely used treatment for inoperable hepatocellular carcinoma (HCC), but its efficacy remains controversial. It has been reported to be effective in prolonging survival in several retrospective series [1–6]. However, prospective randomized trials have so far failed to demonstrate a significant survival benefit [7–9]. The antitumor effect of TACE may be counteracted by the detrimental effect of

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Accepted 23 October 1999

associated treatment morbidity, in particular liver failure [8]. Hence it is important to evaluate treatment-related morbidity and mortality when assessing the efficacy of TACE. While the complications of TACE are well known [10,11], the overall treatment morbidity and mortality rates associated with TACE have not been well documented in the literature.

TACE is also used for the treatment of postoperative intrahepatic recurrence after resection of HCC, but there were only a few reports on the results of TACE for postresection recurrent HCC [12–16]. In particular, there is little data on the morbidity and mortality from TACE in this group of patients. A study was performed to evaluate in detail the treatment morbidity, mortality, long-term survival results, and prognostic factors of TACE in patients with primary inoperable or postresection recurrent HCC based on a prospectively collected database of patients managed in a single institution in a 9-year period.

MATERIALS AND METHODS

Between January 1989 and December 1997, 1,338 patients with newly diagnosed HCC were managed in the Department of Surgery of the University of Hong Kong at Queen Mary Hospital. Of these, 1,008 patients were inoperable because of advanced tumors or inadequate liver reserve. TACE was used as the treatment of choice for inoperable HCC whenever possible and was given in 384 (38%) patients. Percutaneous ethanol injection therapy (PEIT) was given to 12 patients with tumors < 3 cm, in whom TACE was not possible because of significant arteriovenous shunting or technical reasons. Systemic chemotherapy was given to 87 patients who had extrahepatic metastasis or main portal vein thrombosis but were in good general condition. The other 525 patients were managed conservatively with supportive care.

Hepatectomy was performed in 330 patients (25%), and subsequently intrahepatic recurrence developed in 148 patients during the study period. Intrahepatic recurrence was detected by regular postoperative surveillance, including monthly alpha fetoprotein (AFP) level and 3-monthly ultrasonography or computed tomography (CT) scan. Suspected recurrence was confirmed by angiography and postlipiodol CT scan and if necessary by fine-needle aspiration cytology. Only 12 (8%) of 148 patients had recurrent tumors amenable to reresection. One-hundred patients were treated with TACE for intrahepatic recurrence. The median interval from resection to recurrence in these patients was 6 months (range 1–57 months). Sixty-eight patients had major resection as defined by resection of 3 or more segments, and 32 had minor resection of 2 segments or less. These patients were not suitable for repeat hepatectomy because of inadequate liver reserve, multifocal recurrence, or recurrence in an unfavorable position. Other treatment for patients with unresectable intrahepatic recurrence included PEIT in 10, systemic chemotherapy in 9, and supportive care in 17 patients.

The selection criteria for TACE were the same for inoperable HCC and postresection recurrence including: 1. absence of extrahepatic metastasis; 2. patent main portal vein; 3. serum bilirubin level < 50 umol/L; 4. Child's A or B liver status; and 5. absence of significant arteriovenous shunting. TACE was offered even for large tumors provided the above criteria were met. All TACE procedures were performed by experienced interventional radiologists. During the procedure, 10 ml of lipiodol was mixed with 10 mg of cisplatin into a 20 ml emulsion. Depending on the tumor size, between 4 ml and 60 ml of the emulsion was infused into the liver through a catheter placed into a branch of the hepatic artery supplying the tumor or into the hepatic artery proper beyond the gastroduodenal artery for bilobar or multifocal disease. Light embolization of the feeding artery was then performed using small gelfoam pellets of 1×1 mm size mixed with 40 mg gentamycin. Gelfoam injection was stopped when the blood flow in the artery supplying the tumor slowed down but before occlusion occurred. Prophylactic antibiotic and H2 blocker were given for 5 days after the procedure.

TACE was repeated at regular intervals between 8–12 weeks. Patients had close follow-up after TACE with monthly renal, liver function tests, and serum AFP level. Tumor response was assessed by angiography during each subsequent TACE session and by 3-monthly CT scan. Tumor response was categorized according to the World Health Organization criteria [17]: complete response, disappearance of all lesions detected by imaging; partial response, $\geq$ 50% decrease in tumor size; no change, < 50% decrease in tumor size or < 25% increase in tumor size; progressive disease, $\geq$ 25% increase in tumor size or appearance of new lesions. Further TACE would be terminated if there was evidence of liver failure (bilirubin > 50 umol/L, ascites uncontrolled by diuretics or hepatic encephalopathy), other major complications, progression of disease, or development of extrahepatic metastasis.

Clinicopathologic data of all patients have been prospectively collected in a computerized database since 1989. The characteristics of the patients at the time of first TACE treatment are shown in Table I. The main differences between patients with recurrent HCC and those with primary inoperable tumors were the much smaller mean tumor size and better liver function (serum albumin and bilirubin levels) in the former group. Treatment results including tumor response and any morbidity or mortality were entered into the database after each TACE treatment. Only significant complications were analyzed for morbidity. Common minor side effects such as fever, vomiting, and abdominal pain after TACE were excluded. Treatment-related mortality was defined as

TABLE I. Clinicopathologic Data of 484 Patients Treated With Transarterial Chemoembolization

	Inoperable HCC (n = 384)	Recurrent HCC (n = 100)
Gender, male/female	327/57	87/13
Age, years	57.4 ± 13.1	53.2 ± 12.6
HBsAg status		
Positive	311 (81%)	83 (83%)
Negative	73 (19%)	17 (17%)
Serum albumin		
≤35 g/L	114 (30%)	21 (21%)
>35 g/L	270 (70%)	79 (79%)
Serum bilirubin		
≤20 umol/L	270 (70%)	81 (81%)
>20 umol/L	114 (30%)	19 (19%)
Child's grading		
A	314 (82%)	84 (84%)
B	70 (18%)	16 (16%)
Tumor size, cm	7.9 ± 3.8	2.6 ± 1.3
Serum AFP		
≤20 ng/ml	82 (21%)	46 (46%)
>20 ng/ml	302 (79%)	64 (64%)
Tumor pattern		
Solitary	223 (58%)	52 (52%)
Multinodular	69 (18%)	42 (42%)
Diffuse	92 (24%)	6 (6%)

HCC = hepatocellular carcinoma; HBsAg = hepatitis B surface antigen; AFP = alpha fetoprotein.

death resulting from a complication within 30 days after the procedure.

The following factors at the time of first TACE treatment were analyzed for prognostic significance among the 484 patients: sex, age (≤ 60 or > 60 years), hepatitis B surface antigen status (positive or negative), serum albumin level (≤ 35 or > 35 g/L), serum bilirubin level (≤ 20 or > 20 umol/L), Child's grading (A or B), serum AFP level (≤ 20 or > 20 ng/ml), tumor size (≤ 10 or > 10 cm), tumor pattern (solitary, multinodular, or diffuse), and nature of the tumor (primary inoperable or postresection recurrent tumor).

Numerical data were expressed as mean and standard deviation (SD). Categorical variables were compared using the Chi-square test or Fisher exact test where appropriate, and continuous variables were compared using the unpaired *t*-test. Survival curves were computed using the Kaplan-Meier method, and groups were compared using the Log rank test. Univariate analysis, followed by multivariate analysis using Cox proportional hazards model, was performed to identify prognostic factors of survival after TACE treatment. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

An average of 3.5 sessions of TACE (SD 3.9, range 1–27) were given among 484 patients. The overall treatment-related morbidity and mortality rates were 23% (112/484) and 4.3% (21/484), respectively (Table II). The morbidity rate for patients with primary inoperable HCCs and postresection recurrent tumors was 25% (97/384) and 15% (15/100), respectively, and the mortality rate was 5.2% (20/384) and 1% (1/100), respectively. Liver failure was the most common complication, causing 14 of the 21 treatment-related deaths. Compared with patients who were not complicated by liver failure, patients with post-TACE liver failure had significantly larger tumor size (mean 11.2 cm vs. 6.1 cm, $P < 0.001$), worse pretreatment liver function (mean serum albumin 30.4 g/L vs. 39.2 g/L, $P = 0.018$), and received a higher dose of lipiodol-cisplatin emulsion (mean 28.5 ml vs. 16.2 ml, $P = 0.022$). Other causes of treatment-related mortality included tumor rupture (5), perforated duodenal ulcer (1), and renal failure (1). In patients complicated by tumor rupture, the tumor size ranged from 8 cm to 17 cm, and the rupture occurred within 2 weeks after the TACE treatment in all cases.

TABLE II. Morbidity and Mortality Related to Transarterial Chemoembolization Among 484 Patients

Morbidity	
Liver abscess	8 (1.6%)
Rupture of tumor	6 (1.2%)
Acute cholecystitis	1 (0.2%)
Acute pancreatitis	2 (0.4%)
Gastrointestinal bleeding	11 (2.3%)
Peptic ulcer	11 (2.3%)
Liver failure	71 (15%)
Others*	26 (5.4%)
Any complication (s):	112 (23%)
30-day mortality	21 (4.3%)

Figures indicate number of patients with morbidity or mortality after any one treatment session.
*Other complications included renal failure, pancytopenia, and complications related to femoral artery catheterization.

To further analyze the effects of tumor size and pretreatment liver function on treatment mortality, the patients were stratified by the tumor size and serum albumin level into 4 groups: A, tumor ≤ 10 cm, serum albumin > 35 g/L; B, tumor ≤ 10 cm, serum albumin ≤ 35 g/L; C, tumor > 10 cm, serum albumin > 35 g/L; D, tumor > 10 cm, serum albumin ≤ 35 g/L. The treatment mortality rate in groups A, B, C, and D was 1.8% (5/277), 4.4% (4/90), 4.2% (3/72), and 20% (9/45), respectively. The mortality rate in group D was significantly higher than the other groups, but the differences among groups A, B, and C were not significant.

Twenty-three (4.8%) of 484 patients were lost to follow-up. Of the remaining 461 patients with complete follow-up data, complete response was observed in 11 patients (2%), partial response at least initially was observed in 218 patients (48%), and 232 patients (50%) had either no change or progressive disease. The overall 1-year, 3-year, and 5-year survival rates from the time of

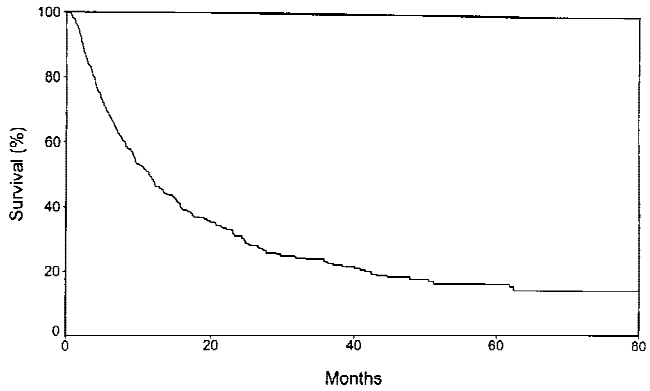

Fig. 1. Overall survival curve in patients with primary inoperable or postresection recurrent HCC treated with TACE.

first TACE treatment were 49%, 23%, and 17%, respectively (Fig. 1). The 1-year, 3-year, and 5-year survival rates for patients with primary inoperable tumors were 44%, 20%, and 15%, respectively, and for patients with postresection recurrent tumors were 69%, 37%, and 22%, respectively.

Five factors at the time of first TACE treatment were found to have prognostic significance by univariate analysis, including serum albumin level, serum AFP level, tumor size, tumor pattern, and nature of the tumor (Table III). After multivariate analysis, serum albumin ≤ 35 g/L (risk ratio [RR] = 1.5013; 95% confidence interval [CI] 1.0280–2.4366; $P = 0.032$) and tumor size > 10 cm (RR = 2.5466; 95% CI 1.8456–3.7326; $P < 0.001$) were the only significant adverse prognostic factors. Using the same stratification as for mortality analysis, the 1-year, 3-year, and 5-year survival rates for group A patients were 59%, 30%, and 21%, respectively; for group B patients were 44%, 20%, and 16%, respectively; for group C patients were 33%, 14%, and 10%, respectively; and for group D patients were 23%, 5%, and 0%, respectively.

TABLE III. Prognostic Factors of Long-Term Survival by Univariate Analysis

	Median survival (months)	*P* value
Serum albumin		
≤35 g/L (n = 135)	6.0	0.004
>35 g/L (n = 349)	14.0	
Serum AFP		
≤20 ng/ml (n = 118)	16.5	<0.001
>20 ng/ml (n = 366)	7.8	
Tumor size		
≤10 cm (n = 367)	14.6	<0.001
>10 cm (n = 117)	5.6	
Tumor pattern		
Solitary (n = 275)	12.5	0.024
Multinodular (n = 111)	10.2	
Diffuse (n = 98)	7.4	
Nature of tumor		
Primary inoperable (n = 384)	9.0	<0.001
Postresection recurrence (n = 100)	24.2	

AFP = alpha fetoprotein.

DISCUSSION

Resection is the main hope of cure for HCC but is possible in only a small proportion of patients because HCC is usually advanced at presentation and is frequently associated with cirrhosis. Only 25% of patients referred to our department had resectable tumors. For patients with inoperable HCC, the best treatment remains controversial. TACE is a widely adopted treatment modality and has been used as the treatment of choice in our institution over the past years.

An analysis of the treatment results from our prospectively collected database indicated that TACE in patients with inoperable HCC was associated with substantial rates of severe complications and treatment-related mortality, despite strict adherence to standardized selection criteria and treatment protocol. Our selection criteria were similar to those used by other authors [4,6,8]. In accordance with others' experience, liver failure was the most common cause of morbidity and mortality [8,18]. Our results revealed that liver failure occurred more frequently in patients with large tumor size and was related to the dose of cisplatin given. Patients with a poor pretreatment liver function as indicated by a low serum albumin level were also more prone to liver failure after TACE treatment. Other authors have shown that the liver function status is an important determinant of the risk of liver failure [18,19]. Another remarkable complication in this group of patients was rupture of HCC after TACE treatment, and 5 of the 6 patients with tumor rupture died of the complication. All of these patients had large tumors. The mechanism of rupture is unclear, but it may be related to tumor necrosis and increased pressure inside a large tumor after TACE treatment. The high incidence of liver failure and other severe complications has compromised the long-term survival directly by leading to mortality and indirectly by precluding further TACE. Repetition of TACE is considered important to prolong survival [3,6]. In view of the substantial morbidity and mortality related to TACE treatment, stricter criteria for selection of patients may be appropriate. Based on our analysis of the treatment-related mortality, patients with a tumor size > 10 cm together with a pretreatment serum albumin level ≤ 35 g/l had a very high treatment mortality rate (20%), suggesting that this subgroup of patients might not be suitable candidates for TACE treatment.

Randomized trials on TACE or transarterial embolization for inoperable HCC have so far failed to prove any survival benefit compared with patients receiving only conservative treatment [7–9]. Notwithstanding, the role of TACE in the management of inoperable HCC has not

been fully clarified yet, as these trials have been criticized for the heterogeneity of the enrolled patients, difference in TACE techniques, and methodological drawbacks such as insufficient statistical power [20]. It has also been suggested that further randomized trials should be performed in subgroups of patients expected to have better prognosis [20]. In our study, poor liver function (serum albumin level $\leq$ 35 g/L) and tumor size > 10 cm were the main adverse prognostic factors of long-term survival. The same two factors were associated with a high treatment mortality rate, indicating a major influence of treatment mortality on the overall survival results with TACE treatment. Tumor size is also the main determinant of tumor response to TACE [19,21]. Our results suggested that stricter selection criteria in terms of liver function and tumor size could reduce treatment-related mortality and improve long-term survival.

Satisfactory results have been observed with TACE treatment in patients with intrahepatic recurrence after previous hepatic resection. TACE in patients after previous hepatectomy could theoretically present problems such as anatomic distortions due to operation and damage to nontumorous tissue in the liver remnant [14]. However, our results demonstrated relatively low morbidity and mortality rates and favorable long-term survival rates after TACE treatment. The better outcome in this group of patients compared with patients with primary inoperable HCCs was largely related to the small tumor size at the time of TACE treatment. The importance of regular surveillance after resection of HCC for early detection of recurrence could not be overemphasized. These patients had been carefully screened to ensure adequate liver function reserve before hepatectomy, and even after major resection, most patients maintained a satisfactory liver function. This may be another factor contributing to the favorable results in these patients.

The high incidence of intrahepatic recurrence after hepatectomy in our patients is in accordance with the findings of other authors [22,23]. Currently there is no effective measure to prevent recurrence, and aggressive management of recurrence seems to be the best way to improve the long-term outcome following resection of HCC [24]. Reresection is considered the treatment of choice for intrahepatic recurrence [25]. However, the reresectability rate is usually low. In our series reresection was possible in only 8% of patients because the majority had previous major resection, inadequate liver reserve, or multinodular recurrence. Our study shows that TACE is applicable to the majority of patients with intrahepatic recurrence with favorable results. However, a randomized trial would be required to confirm the effectiveness of TACE for postresection recurrence. PEIT has been used as an alternative treatment for recurrent HCC [26], and recently a combination of TACE and PEIT has been reported to produce better results than TACE alone [27]. The benefit of this approach needs further evaluation.

In conclusion, this study shows that TACE for inoperable HCC with the current selection criteria was associated with significant morbidity and mortality, which limited the survival benefit. Better patient selection in terms of tumor size and liver function is required to improve treatment results. Based on the results of this study, a simple staging system in relation to TACE treatment for HCC could be proposed. Stage I patients have tumors $\leq$ 10 cm and serum albumin level > 35 g/L. TACE in these patients was associated with a low treatment mortality rate and favorable long-term survival results. Stage II patients have either tumors $\leq$ 10 cm with serum albumin $\leq$ 35 g/L or tumors > 10 cm with serum albumin > 35 g/L. TACE in these patients resulted in an intermediate but acceptable mortality and survival outcome. Stage III patients have tumors > 10 cm and serum albumin level $\leq$ 35 g/L. TACE in these patients resulted in a high treatment mortality rate and poor survival results. It appears that this group of patients may not be suitable candidates for TACE treatment. Unfortunately, so far no other treatment modalities have been found useful in these patients with large HCC and poor liver function reserve, and an effective treatment for these patients remains to be searched. Further randomized studies of TACE should focus on selected patients who are more likely to benefit from the treatment in terms of tumor size and liver function.

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